is inhaled and thus contacts the lower respiratory tract (lungs). The absorption enhancer improves pulmonary absorption of the polypeptide.

Claims 1-22, and 26-32 are pending. Applicants hereby affirm the election of Group I, claims 1-22 and 26-30. Claims 23-25 have been cancelled without prejudice by the above amendment, as being drawn to a non-elected invention. The specification and claims 2, 4, 12, and 27 have been amended to correct typographical errors and to specify that the analogues are polypeptide analogues. The latter amendments simply make explicit what is implied by the polypeptide limitations of claims 1 and 3. Claim 2 has also been amended to include a coarse particle size limitation of at least 20 microns in diameter. Support for this amendment is found, for example, in the specification at page 3, lines 16-26. Support for new claims 31 and 32 may be found, for example, in the specification, page 11, lines 14-15. In the specification, a few typographical errors and a misformatted Table I have been corrected, and certain abbreviations replaced with complete terms. No new matter has been introduced as a result of the above amendments.

Claims 1-22 and 26-30 were rejected on various grounds. Reconsideration of these claims and consideration of new claims 31 and 32 are respectfully requested in view of the following remarks.

Rejection under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 2, 4, 12, and 27 under 35 U.S.C. §112, ¶2, for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention (Office Action, page 3, lines 12-14). This rejection is traversed below on a claim-by-claim basis.

According to the Examiner, there are two confusing terms in claim 2. First, "resultant powder" is said to be confusing for lack of antecedent basis or lack of a process by which the powder results (Office Action, page 3, lines 15-16). Claim 2 has been amended accordingly by replacing "resultant powder" with --said mixture--.

The Examiner also stated that the particle size range encompassed by the term "coarse particles" is unclear (Office Action, page 3, lines 16-17). This rejection is overcome by the amendment to claim 2, limiting the coarse particles to those having a diameter of at least 20 microns.

According to the Examiner, claims 4 and 27 are indefinite for two reasons (Office Action, page 4, lines 1-4). First, the Examiner objects to the recited abbreviations such as hANP, GnRHa, and TRHrh as indefinite. Both the claims and the specification have been amended to indicate more clearly that hANP is human atrial natriuretic peptide and that TRHrh is recombinant human thyroxine releasing hormone.

Second, the Examiner asked what limitations are placed on "analogs" of gonadotropin agonists or somatostatin (Office

Action, page 4, lines 5-6). Claims 4 and 27 have now been amended to specify that the analogs are polypeptide analogs. Applicants respectfully submit that it is understood in the art that polypeptide analogs of a given polypeptide are functional analogs, which often but do not always have a high degree of structural similarity to the native compound. Art-recognized analogs are straightforward to obtain via standard synthetic or biosynthetic routes, or from commercial vendors.

In claim 12, the Examiner found the term "bile salt derivative" to be unclear (Office Action, page 4, lines 7-9). Bile salts are anionic carboxylates with counter-cations such as sodium, potassium, or an organic amine (specification, page 4, lines 32-33). It is well known in the art, and arguably trivial, to prepare derivatives of bile salts by substituting one counter-cation for another, or by preparing an ester derivative of the carboxylate, for example.

For the reasons stated above, it is believed that the rejections of claims 2, 4, 12, and 27 under 35 U.S.C. §112, ¶2, have been overcome. Applicants respectfully request that these rejections be withdrawn.

Rejection under 35 U.S.C. §102(e)

The Examiner rejected claims 1-14, 17-22, and 26-29 under 35 U.S.C. §102(e) as anticipated by Platz et al. (U.S. Pat. No. 5,284,656) ("Platz"). The Examiner stated (Office Action, page 5, lines 22-24, emphasis added):

> Platz et al. disclose pharmaceutical compositions containing a pharmaceutically active polypeptide and an absorption enhancer for administration via a dry powder inhaler device which are identical to those disclosed by applicants.

This rejection is traversed on the grounds that Platz does not disclose a dry powder formulation which includes a polypeptide and an absorption enhancer, all of which are limitations in all of the rejected claims.

Platz describes three formulations of granulocyte colony-stimulating factor (G-CSF):

(1) G-CSF dissolved in water with a buffer, a simple sugar for protein stabilization, and a surfactant such as polyoxyethylene fatty acid esters "to reduce or prevent surface induced aggregation of the protein" (column 3, line 46 - column 4, line 3);

(2) G-CSF provided in a powder "suspended in a propellant with the aid of a surfactant," such as oleic acid or soya lecithin (column 4, lines 4-17); and

(3) G-CSF provided in a powder with a bulking agent such as lactose or sorbitol "which facilitates dispersal of the powder from the device" (column 4, lines 19-26).

None of these formulations is a dry powder mixture of a pharmaceutically active polypeptide and an absorption enhancer. Formulation (1) is an aqueous solution and therefore cannot be a dry powder mixture. Formulations (2) and (3) both lack an absorption enhancer. Indeed, Platz states (at column 2, lines 48-60, emphasis added):

> The present invention is based on the discovery that G-CSF can be administered systemically to a mammal via the pulmonary route. [...] Importantly and surprisingly, substantial amounts of G-CSF are thereby deposited [...]. Moreover, this is accomplished without the necessity to resort to special measures such as the use of absorption enhancing agents or protein derivatives specifically designed to improve absorption.

In other words, Platz intended to exclude absorption enhancers from his formulations. The "surfactant" described by Platz in formulation (2) is intended to improve suspension of the powdered G-CSF in the liquid propellant, and not to promote absorption of G-CSF. Moreover, both soya lecithin (which includes acid esters of linoleic and oleic acids) and oleic acid are oils, in other words, liquids which cannot be formulated into a dry powder. Since the claims require that both of the "active compounds" be in powder form, clearly neither of these oils could constitute an absorption enhancer as recited in the claims. Since Platz fails to teach a dry powder formulation which includes an absorption enhancer, it does not anticipate any of Applicants' claims.

In view of the above, the rejection of claims 1-14, 17-22, and 26-29 under 35 U.S.C. §102(e) as anticipated by Platz is unwarranted. Applicants respectfully request that this rejection be withdrawn.

Rejection under 35 U.S.C. §103

Claims 1-22 and 26-30 were rejected under 35 U.S.C. §103 as discussed below.

I.

In the alternative to a rejection under 35 U.S.C. §102(e), the Examiner rejected claims 1-14, 17-22, and 26-29 under 35 U.S.C. §103 as unpatentable over Platz. This rejection is traversed. As discussed in the preceding subsection, Platz describes three formulations, none of which is a dry powder formulation which includes a polypeptide and an absorption enhancer. Indeed, when describing the formulations of his invention, Platz emphasizes the absence of "absorption enhancing agents" (column 2, lines 56-60). Since Platz unequivocally teaches away from the present invention, none of the claims can be said to be "obvious" over this reference.

In view of the above, Applicants request withdrawal of the rejection of claims 1-14, 17-22, and 26-29 under U.S.C. §103 as unpatentable over Platz.

II.

The Examiner rejected claims 1-3, 5-11, 17, 18, 21, 22, 26, and 28 under 35 U.S.C. §103 as unpatentable over Rubsamen (U.S. Pat. No. 5,364,838) in view of Platz (Office Action, page 6, lines 17-19). This rejection is respectfully traversed on the grounds that, even in combination, the cited references do not teach or suggest an inhalable dry powder formulation which includes a polypeptide and an absorption enhancer.

Regarding the primary reference, the Examiner stated (Office Action, page 7, lines 1-4, emphasis added):

> Rubsamen discloses pharmaceutical compositions containing a pharmaceutically active polypeptide and an absorption enhancer, and methods of introducing biologically active polypeptides into the lower respiratory tract of a subject as a dry powder in the presence or absence of a surfactant absorption enhancer via an inhaler device.

In other words, the Examiner relied on Rubsamen to teach a dry powder formulation for the lower respiratory tract which includes a polypeptide and an absorption enhancer.

Applicants respectfully submit that the Examiner has misread Rubsamen on this point. While Rubsamen does teach certain insulin-containing formulations for delivery via the lungs, none constitutes a dry powder formulation containing both insulin and an absorption enhancer. Rubsamen says at col. 14, lines 40 *et seq*. that there are "four basic types of insulin formulations" useful in his inhaler invention:

(1) powdered insulin suspended, with an excipient, in a low boiling point, highly volatile propellant supplied under pressure;

(2) insulin dissolved in an aqueous solution which is suspended, with an excipient, in a low boiling point, highly volatile propellant supplied under pressure;

(3) insulin "provided as a dry powder by itself"; and

(4) insulin provided in a solution.

He also mentions, at column 16, lines 1-5, a fifth type of formulation: liposomes containing insulin. This fifth type, as well as formulations (2) and (4) above, plainly have no relevance to the present claims, because (a) they do not involve a dry

powder, and (b) they utilize no absorption enhancer. Rubsamen's teaching with respect to formulation (3), insulin "by itself", cannot be read as suggesting that an absorption enhancer or any other active (or inactive) ingredient should be included. Nor does Rubsamen's formulation (1) suggest the claimed invention. The absorption enhancer specified in the claims must be in the form of a dry solid at room temperature if it is to form, together with insulin, a "dry powder suitable for inhalation", as required by the claims. Rubsamen's preferred "excipient" for use in his formulation (1), oleic acid, is an <u>oil</u> at room temperature (column 15, lines 50-53). Again, since an oil is a liquid that obviously cannot be formulated as a powder, oleic acid is not an absorption enhancer potentially useful in the claimed therapeutic preparation. Furthermore, Rubsamen does not teach use of any specific "excipients" other than oils. There is no reason to believe that in general an excipient, defined as "any more or less inert substance added to a prescription in order to confer a suitable consistency or form to the drug; a vehicle,"[1] and included by Rubsamen for the sole purpose of "allowing suspension of the insulin with the propellant" (column 15, lines 48-50), would meet the criteria for the absorption enhancer set forth in claim 1.

Rubsamen's failure to include an absorption enhancer any of his proposed insulin formulations is not surprising, because Rubsamen's own invention "endeavors to overcome the

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[1] DORLAND'S MEDICAL DICTIONARY (26th ed., 1985) page 473.

problems of the prior art by eliminating the need for permeation enhancers (column 2, lines 57-59)." Rubsamen points out that insulin formulations for nasal administration which include certain "penetration enhancers" (i.e., absorption enhancers) have been demonstrated to cause nasal mucosal irritation in man (column 1, lines 43-62), which would only be exacerbated by the continuous treatment necessary for chronic diabetes. Second, Rubsamen notes that no nasally-administered formulations which include penetration enhancers have been commercialized (column 1, lines 62-68). Turning to delivery of insulin to the lower respiratory tract, Rubsamen reasons:

> [...] Because the surface area of membranes available to absorb insulin is much greater in the lung than in the nose, no membrane penetration enhancers are required for delivery of insulin to the lungs by inhalation. Column 2, lines 7-10.

By arguing thus that penetration enhancers are not only unnecessary but in fact should be avoided, Rubsamen literally teaches away from Applicants' invention.

Nor does the secondary reference cited by the Examiner, Platz, supply a teaching which satisfies the deficiencies in Rubsamen. As discussed above, regardless of what else Platz may teach or suggest,[2] Platz fails to teach or suggest an inhalable dry powder formulation which includes a polypeptide and an absorption enhancer. Like Rubsamen, and as discussed above, Platz teaches away from the present invention by asserting that

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[2] The Examiner relied on Platz for the teaching of particles having a diameter of less than 10 microns (Office Action, page 7, lines 4-7).

an absorption enhancer is not necessary for the pulmonary delivery of a polypeptide. Thus, the invention as recited in claim 1 or any of the other claims cannot be said to be obvious in view of these references. Applicants therefore respectfully request withdrawal of the rejection of claims 1-3, 5-11, 17, 18, 21, 22, 26, and 28 under 35 U.S.C. §103 as unpatentable over Rubsamen in view of Platz.

III.

The Examiner rejected claims 1, 2, 6-18, 21, 22, and 28-30 under 35 U.S.C. §103 as unpatentable over Rubsamen (U.S. Pat. No. 5,364,838) in view of Clark et al. ("Clark") (U.S. Pat. No. 5,341,800) and further in view of Edman et al. ("Edman") (Advanced Drug Delivery Reviews 8:165-177 1992) and Mishima et al. ("Mishima") (J. Pharmacol.-Dyn. 10:624-631 1987) (Office Action, page 7, lines 11-14). This rejection is traversed on the grounds that the cited art, even in combination, fails to teach or suggest an inhalable dry powder formulation which includes a polypeptide and a substance which enhances absorption of the polypeptide in the lungs.

Rubsamen, the primary reference, has been discussed above in subsection II.

Clark, a secondary reference, is merely a mechanical device patent which discloses an inhalation device. Regardless of what else Clark may teach or suggest, Clark fails to teach or suggest inhalable dry powder formulations which include a polypeptide and an absorption enhancer.

With respect to Edman and Mishima, the Examiner stated (Office Action, page 8, lines 4-7):

> [...] Edman et al. disclose the use of bile salts, phospholipids, alkyl glycosides, cyclodextrins, or fatty acids as absorption enhancers, and Mishima discloses the use of capric acid or its salt as an absorption enhancer [...].

However, the Examiner fails to note two defects regarding Edman and Mishima in the context of Rubsamen. First, Edman and Mishima are concerned entirely with absorption through the nasal mucosa. In contrast, Rubsamen's teachings concern delivery through the lower respiratory tract, as does Applicants' claim 1. Edman and Mishima are, therefore, far less relevant to the present invention than Rubsamen. As discussed above, it is Rubsamen's strongly expressed view that absorption enhancers are unnecessary and undesirable in insulin formulations intended for pulmonary administration. Second, Rubsamen is a more recent reference than either Edman or Mishima. Therefore, Rubsamen's teachings presumptively override, or at least neutralize, those of Edman and Mishima. Rubsamen teaches that, as a likely result of mucosal irritation, the use of absorption enhancers in nasal formulations has not produced an acceptable means for treating diabetes. Thus, one of ordinary skill, reading the references cited by the Examiner, would derive from these references a teaching that one should avoid the use of absorption enhancers in formulations designed for pulmonary administration.

For the reasons stated above, the combination of the cited references fails to teach or suggest a dry powder

formulation suitable for inhalation which includes a polypeptide and a substance which enhances absorption of the polypeptide in the lungs. It is therefore believed that the rejection of claims 1, 2, 6-18, 21, 22, and 28-30 under 35 U.S.C. §103 in view of the cited art should be withdrawn.[3]

Provisional Rejection under 35 U.S.C. §101.

The Examiner provisionally rejected claims 1, 2, and 6-19 under 35 U.S.C. §101 as claiming the same invention as that of claims 1-33 of copending application Serial No. 08/265,372. (Office Action, page 8, lines 15-18).

Applicants respectfully traverse this rejection. Unlike the present claims, the claims of the 08/265,372 application are specifically limited to insulin-containing formulations. A double patenting rejection is proper only where the two applications claim precisely the same invention. As explained in the Manual of Patent Examining Procedure, §804, "same invention" means identical subject matter. Miller v. Eagle Mfg. Co., 151 U.S. 186 (1984); In re Ockert 114 USPQ 330 (C.C.P.A. 1957); and In re Vogel, 164 USPQ 619 (C.C.P.A. 1970). As explained in the M.P.E.P., if there is an embodiment of a claim of one application that does not fall within a claim of the second application, statutory double patenting under 35 U.S.C. §101 does not exist. In the present case, there are many

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[3] New claims 31 and 32 depend from claim 1, and thus include the limitations recited therein. For the same reasons discussed in this section, claims 31 and 32 are therefore also nonobvious.

embodiments of claim 1 of the present application which do not fall within any of the claims of the 08/265,372 application; e.g., where the polypeptide is vasopressin, an interleukin, human growth hormone, or any other polypeptide except insulin. The 08/265,372 application therefore does not claim the "same invention" as the present application. A double-patenting rejection is improper, and Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

It is submitted that all pending claims are in condition for allowance, and such action is respectfully requested. Please apply any additional charges, or credits, to Deposit Account No. 06-1050.

Respectfully submitted,

Date: Nov. 6, 1995

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